

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BUSH *et al*

Appl. No. 09/380,704

Filed: September 8, 1999

For: **Identification of Agents for Use in
the Treatment of Alzheimer's
Disease**

Art Unit: To be assigned

Examiner: To be assigned

Atty. Docket: 0609.4350001/REF/KKV

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Information Disclosure Statement

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. A copy of each of documents AA1-AC1, AF1, AG1, AI1, AK1, AL1-AN1, AI2-AK2, AN2, AO2, AI3, AK3, AL3, AI4-AK4, AP4, AI5, AJ5, AL5-AP5, AL6-AN6, AP6, AL7-AP7, AL8, AN8, AL9, AO9, AP9, AL10, AM10, AO10, AP10, AL11, AN11, AL12, AP12, AL13, AN13-AP13, AL14, AM14, AP14, AN15-AP15, AL16-AO16, AL17, AN17, AO17, AN18-AO18, AL19-AP19, AL20, AN20, AP20, AM21, AO21, AP21, AM22, AN22, AM23, AO23, AP23, AM24-AP24, AL25-AP25, AL26, AM26, AP26, AN27, AO27, AP27, AM28-AP28, AL29-AP29, AL30, AP30, AL31, AM31, AP31, AL32, AM32, AL33-AO33 is provided. The remaining documents were previously cited or copies were submitted in Applicants' 35 U.S.C. § 120 priority Application No. 08/816,122, filed March 11, 1997.

Document AN16 and AP29 are in a non-English language. An English language abstract for document AN16 is located on page 1378 of document AN16.

JAN 18, 2000

Document AN16 appears to show mass spectrometry of 5-chloro-7-iodo-8-quinolono-
metal chelates.

Document AP29 appears to show the neurotoxicity of Clioquinol and the
autoradiographic distribution of radioactive Clioquinol in several species of animals.

The Examiner's attention is directed to co-pending U.S. Patent Application Nos.
09/038,154 filed March 11, 1998, and 09/224,953, filed January 4, 1999, which are directed
to related technical subject matter. The identification of these U.S. Patent Applications is not
to be construed as a waiver of secrecy as to those applications now or upon issuance of the
present application as a patent. The Examiner is respectfully requested to consider the cited
applications and the art cited therein during examination

Where the publication date of a listed document does not provide a month of
publication, the year of publication of the listed document is sufficiently earlier than the
effective U.S. filing date and any foreign priority date so that the month of publication is not
in issue. Applicants have listed publication dates on the attached PTO-1449 based on
information presently available to the undersigned. However, the listed publication dates
should not be construed as an admission that the information was actually published on the
date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over
any of the information provided herewith, and/or to prove that this information may not be
prior art, and/or to prove that this information may not be enabling for the teachings
purportedly offered.

This statement should not be construed as a representation that a search has been made,
or that information more material to the examination of the present patent application does not
exist. The Examiner is specifically requested not to rely solely on the material submitted

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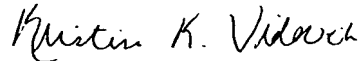
herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120, 1138 OG 37, 38 (May 19, 1992).

This Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. No statement or fee is required.

It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449 and indicate in the official file wrapper of this patent application that the documents have been considered. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this pleading is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA1	5,242,932	09/07/1993	Gandy <i>et al.</i>	514	313	12/17/1991
	AB1	5,373,021	12/13/1994	Marangos	514	483	04/26/1993
	AC1	5,523,295	06/04/1996	Fasman	514	63	07/06/1994
	AD1	5,688,516	11/18/1997	Raad <i>et al.</i>	424	409	10/03/1994
	AE1	5,688,651	11/18/1997	Solomon	435	7.1	12/16/1994
	AF1	5,705,401	01/06/1998	Masters <i>et al.</i>	436	518	09/16/1994
	AG1	5,707,821	01/13/1998	Rydel <i>et al.</i>	435	18	06/07/1995
	AH1	5,721,106	02/24/1998	Maggio <i>et al.</i>	435	7.8	09/12/1994

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	A11	WO 92/18111	10/29/1992	WIPO			Yes No
	AJ1	WO 93/10459	05/27/1993	WIPO			Yes No
	AK1	WO 93/24451	12/09/1993	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AL	1	Assaf, S.Y. and Chung, S.-H., "Release of endogenous Zn ²⁺ from brain tissue during activity," <i>Nature</i> 308:734-736 (April 1984).
	AM	1	Atwood, C.S. <i>et al.</i> , "Dramatic Aggregation of Alzheimer A β by Cu(II) Is Induced by Conditions Representing Physiological Acidosis," <i>J. Biol. Chem.</i> 273:12817-12826 (May 1998).
	AN	1	Bacon, P.A. <i>et al.</i> , "Rheumatoid Disease, Amyloidosis and its Treatment with Penicillamine," <i>Eur. J. Rheum. Inflamm.</i> 2:70-74 (1979)
	AO	1	Barrow, C.J., and Zagorski, M.G., "Solution Structures of β Peptide and Its Constituent Fragments: Relation to Amyloid Deposition," <i>Science</i> 253:179-182 (July 1991).
	AP	1	Barrow, C.J., <i>et al.</i> , "Solution Conformations and Aggregational Properties of Synthetic Amyloid β -Peptides of Alzheimer's Disease," <i>J. Mol. Biol.</i> 225:1075-1093 (June 1992).

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							Yes No
	AI2	WO 94/04167	03/03/1994	WIPO			Yes No
	AJ2	WO 95/31199	11/23/1995	WIPO			Yes No
	AK2	WO 96/07096	03/07/1996	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AL	2	Basun, H., <i>et al.</i> , "Metals and trace elements in plasma and cerebrospinal fluid in normal ageing and Alzheimer's disease," <i>J. Neural Transm. [P-D Sect.]</i> 3:231-258 (1991).
	AM	2	Behl, C., <i>et al.</i> , "Hydrogen Peroxide Mediates Amyloid β Protein Toxicity," <i>Cell</i> 77:817-827 (June 1994).
	AN	2	Biaglow, J.E. and Kachur, A.V., "The Generation of Hydroxyl Radicals in the Reaction of Molecular Oxygen with Polyphosphate Complexes of Ferrous Ion," <i>Radiation Res.</i> 148:181-187 (August 1997).
	AO	2	Boado, R.J. <i>et al.</i> , "Drug Delivery of Antisense Molecules to the Brain for Treatment of Alzheimer's Disease and Cerebral AIDS," <i>J. Pharm. Sci.</i> 87(11):1308-1315 (November 1998).
	AP	2	Borman, S., "Diverse Strategies Emerge For Diagnosing Alzheimer's Disease," <i>Chem. Eng. News</i> 272:33-34 (June 1996).

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							Yes
							No
	A13	WO 96/12544	05/02/1996	WIPO			
							Yes
							No
	AJ3	WO 96/28471	09/19/1996	WIPO			
							Yes
							No
	AK3	WO 97/04794	02/13/1997	WIPO			

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AL	<u>3</u>	Bruce, A.J. <i>et al.</i> , "β-Amyloid toxicity in organotypic hippocampal cultures: Protection by EUK-8, a synthetic catalytic free radical scavenger," <i>Proc. Natl. Acad. Sci. USA</i> 93:2312-2316 (March 1996).
	AM	<u>3</u>	Burdick, D., <i>et al.</i> , "Assembly and Aggregation Properties of Synthetic Alzheimer's A4/β Amyloid Peptide Analogs," <i>J. Biol. Chem.</i> 267:546-554 (January 1992).
	AN	<u>3</u>	Burns, J.A., <i>et al.</i> , "Selective Reduction of Disulfides by Tris(2-carboxyethyl)phosphine," <i>J. Org. Chem.</i> 56:2648-2650 (April 1991).
	AO	<u>3</u>	Busciglio, J., and Yankner, B.A., "Apoptosis and increased generation of reactive oxygen species in Down's Syndrome neurons <i>in vitro</i> ," <i>Nature</i> 378:776-779 (December 1995).
	AP	<u>3</u>	Bush, A.I., <i>et al.</i> , "A Novel Zinc(II) Binding Site Modulates the Function of the BA4 Amyloid Protein Precursor of Alzheimer's Disease," <i>J. Biol. Chem.</i> 268:16109-16112 (August 1993).

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							Yes No
	AI4	WO 97/09976	03/20/1997	WIPO			Yes No
	AJ4	WO 97/36885	10/09/1997	WIPO			Yes No
	AK4	WO 98/06403	02/19/1998	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AL	<u>4</u>	Bush, A.I., et al., "Modulation of A β Adhesiveness and Secretase Site Cleavage by Zinc," <i>J. Biol. Chem.</i> 269:12152-12158 (April 1994).
	AM	<u>4</u>	Bush, A.I., et al., "The Amyloid β -Protein Precursor and Its Mammalian Homologues," <i>J. Biol. Chem.</i> 269:26618-26621 (October 1994).
	AN	<u>4</u>	Bush, A.I., et al., "Rapid Induction of Alzheimer A β Amyloid Formation by Zinc," <i>Science</i> 265:1464-1467 (September 1994).
	AO	<u>4</u>	Bush, A.I., et al., Response to "Zinc and Alzheimer's Disease," <i>Science</i> 268:1920-1923 (June 1995).
	AP	<u>4</u>	Butterfield, D.A., et al., " β -Amyloid Peptide Free Radical Fragments Initiate Synaptosomal Lipoperoxidation in a Sequence-Specific Fashion: Implications to Alzheimer's Disease," <i>Biochem. Biophys. Res. Commun.</i> 200:710-715 (April 1994).

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	A15	WO 98/40071	09/17/1998	WIPO			Yes No
	AJ5	WO 99/09981	03/04/1999	WIPO			Yes No
	AK						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AL	<u>5</u>	Butterfield, D.A., <i>et al.</i> , "Aβ(25-35) Peptide Displays H ₂ O ₂ -Like Reactivity Towards Aqueous Fe ²⁺ , Nitroxide Spin Probes, and Synaptosomal Membrane Proteins," <i>Life Sci.</i> 58:217-228 (1996).
	AM	<u>5</u>	Cherny, R.A. <i>et al.</i> , "The Aggregation of Aβ in Human Brain is Mediated by Zinc," <i>Soc. for Neurosci. Abstracts</i> 23:534 (October 1997).
	AN	<u>5</u>	Chong, Y.-H., and Suh, Y.-H., "Aggregation of amyloid precursor proteins by aluminum in vitro," <i>Brain Research</i> 670:137-141 (January 1995).
	AO	<u>5</u>	Colaco, C.A.L.S., <i>et al.</i> , "The role of the Maillard reaction in other pathologies: Alzheimer's disease," <i>Nephrol. Dial. Transplant.</i> 11(Suppl. 5):7-12 (1996).
	AP	<u>5</u>	Connor, J.R. <i>et al.</i> , "A Histochemical Study of Iron, Transferrin, and Ferritin in Alzheimer's Diseased Brains," <i>J. Neurosci. Res.</i> 31:75-83 (January 1992).

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	AL	<u>6</u>	Connor, J.R. <i>et al.</i> , "Ceruloplasmin levels in the human superior temporal gyrus in aging and Alzheimer's disease," <i>Neurosci. Lett.</i> 159:88-90 (September 1993).
	AM	<u>6</u>	Coyle, J.T., and Puttfarcken, P., "Oxidative Stress, Glutamate, and Neurodegenerative Disorders," <i>Science</i> 262:689-695 (October 1993).
	AN	<u>6</u>	Crapper McLachlan, D.R. <i>et al.</i> , "Intramuscular desferrioxamine in patients with Alzheimer's disease," <i>Lancet</i> 337:1304-1308 (June 1991).
	AO	<u>6</u>	Cuajungco, M.P. and Lees, G.J., "Zinc and Alzheimer's disease: is there a direct link?" <i>Brain Res. Rev.</i> 23:219-236 (April 1997).
	AP	<u>6</u>	Dedman, D.J. <i>et al.</i> , "Iron and aluminum in relation to brain ferritin in normal individuals and Alzheimer's-disease and chronic renal-dialysis patients," <i>Biochem J.</i> 287:509-514 (1992).

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	AK						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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AL	Z		Deibel, M.A. <i>et al.</i> , "Copper, iron, and zinc imbalances in severely degenerated brain regions in Alzheimer's disease: possible relation to oxidative stress," <i>J. Neurol. Sci.</i> 143:137-142 (November 1996).
AM	Z		Doré, S., <i>et al.</i> , "Insulin-like growth factor I protects and rescues hippocampal neurons against β -amyloid- and human amylin-induced toxicity," <i>Proc. Natl. Acad. Sci. USA</i> 94:4772-4777 (April 1997).
AN	Z		Dryks, T. <i>et al.</i> , "Amyloidogenicity of β A4 and β A4-bearing Amyloid Protein Precursor Fragments by Metal-catalyzed Oxidation," <i>J. Biol. Chem.</i> 267:18210-18217 (September 1992).
AO	Z		Ehmann W.D. <i>et al.</i> , "Brain Trace Elements in Alzheimer's Disease," <i>NeuroToxicology</i> 7:197-206 (1986).
AP	Z		Esler, W.P., <i>et al.</i> , "Zinc-Induced Aggregation of Human and Rat β -Amyloid Peptides In Vitro," <i>J. Neurochem.</i> 66:723-732 (February 1996).

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	AK						Yes No

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AL	<u>8</u>	Esler, W.P., <i>et al.</i> , "A β deposition inhibitor screen using synthetic amyloid," <i>Nat. Biotechnol.</i> 15:258-263 (March 1997).
AM	<u>8</u>	Fitzgerald, D.J., "Zinc and Alzheimer's Disease," <i>Science</i> 268:1920 (June 1995).
AN	<u>8</u>	Folstein, M. "Nutrition and Alzheimer's Disease," <i>Nutrition Reviews</i> 55:23-25 (January 1997).
AO	<u>8</u>	Fraser, P.E., <i>et al.</i> , "pH-dependent structural transitions of Alzheimer amyloid peptides," <i>Biophys. J.</i> 60:1190-1201 (November 1991).
AP	<u>8</u>	Frederikse, P.H., <i>et al.</i> , "Oxidative Stress Increases Production of β -Amyloid Precursor Protein and β -Amyloid (A β) in Mammalian Lenses, and A β Has Toxic Effects on Lens Epithelial Cells," <i>J. Biol. Chem.</i> 271:10169-10174 (April 1996).

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	AK						Yes No
OTHER (Including Author, Title, Date, Pertinent Pages, etc.)							
	AL	2	Frederickson, C.J., "Neurobiology of Zinc and Zinc-Containing Neurons," <i>Int. Rev. Neurobiol.</i> 31:145-238 (1989).				
	AM	2	Frieden, E., "Ceruloplasmin: A Multi-functional Cupro-protein of Vertebrate Plasma," in: <i>Inflammatory Diseases and Copper</i> , Sorenson, J.R.J., ed., Clifton, N.J.: Humana Press, pp.159-169 (1982).				
	AN	2	Giampaolo, V., "Copper and Inflammation," in: <i>Inflammatory Diseases and Copper</i> , Sorenson, J.R.J., ed., Clifton, N.J.: Humana Press, pp. 329-345 (1982).				
	AO	2	Giulian, D. <i>et al.</i> , "Specific Domains of β -Amyloid from Alzheimer Plaque Elicit Neuron Killing in Human Microglia," <i>J. Neurosci.</i> 16:6021-6037 (October 1996).				
	AP	2	Glenner, G.G., and Wong, C.W., "Alzheimer's Disease: Initial Report of the Purification and Characterization of Novel Cerebrovascular Amyloid Protein," <i>Biochem. Biophys. Res. Commun.</i> 120: 885-890 (May 1984).				
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	AL	<u>10</u>	Golde, I.E., <i>et al.</i> , "Processing of the Amyloid Protein Precursor to Potentially Amyloidogenic Derivatives," <i>Science</i> 255:728-730 (February 1992).
	AM	<u>10</u>	Good, P.F. <i>et al.</i> , "Selective Accumulation of Aluminum and Iron in the Neurofibrillary Tangles of Alzheimer's Disease: A Laser Microprobe (LAMMA) Study," <i>Ann. Neurol.</i> 31:286-292 (March 1992).
	AN	<u>10</u>	Goodman, Y. <i>et al.</i> , "Nordihydroguaiaretic acid protects hippocampal neurons against amyloid β -peptide toxicity, and attenuates free radical and calcium accumulation," <i>Brain Res.</i> 654:171-176 (August 1994).
	AO	<u>10</u>	Goodman, Y., and Mattson, M.P., "Secreted Forms of β -Amyloid Precursor Protein Protect Hippocampal Neurons against Amyloid β -Peptide-Induced Oxidative Injury," <i>Exp. Neurol.</i> 128:1-12 (July 1994).
	AP	<u>10</u>	Gorevic, P.D. <i>et al.</i> , "The Biological Significance of Amyloid," <i>Ann. New York Acad. Sci.</i> 389:380-394 (1982).

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	AL	11	Grundke-Iqbal, I. <i>et al.</i> , "Ferritin is a component of the neuritic (senile) plaque in Alzheimer dementia," <i>Acta Neuropathol.</i> 81:105-110 (December 1990).
	AM	11	Gutteridge, J.M.C., and Wilkins, S., "Copper Salt-Dependent Hydroxyl Radical Formation Damage to Proteins Acting as Antioxidants," <i>Biochim. Biophys. Acta</i> 759:38-41 (August 1983).
	AN	11	Haass, C. <i>et al.</i> , "Amyloid β -peptide is produced by cultured cells during normal metabolism," <i>Nature</i> 359:322-325 (September 1992).
	AO	11	Haley, J.V., "Zinc Sulfate and Wound Healing," <i>J. Surg. Res.</i> 27:168-174 (September 1979).
	AP	11	Halliwell, B., and Gutteridge, J.M.C., "Oxygen toxicity, oxygen radicals, transition metals and disease," <i>Biochem. J.</i> 219:1-14 (April 1984).

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	AL	<u>12</u>	Halliwel, B., "Reactive Oxygen Species and the Central Nervous System," <i>J. Neurochem.</i> 59:1609-1623 (November 1992).
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	AM	<u>13</u>	Hensley, K <i>et al.</i> , "A model for beta-amyloid aggregation and neurotoxicity based on free radical generation by the peptide: Relevance to Alzheimer disease," <i>Proc. Natl. Acad. Sci. U.S.A.</i> 91:3270-3274 (April 1994).
	AN	<u>13</u>	Hensley, K <i>et al.</i> , "Brain Regional Correspondence Between Alzheimer's Disease Histopathology and Biomarkers of Protein Oxidation," <i>J. of Neurochem.</i> 65:2146-2156 (November 1995).
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	AM	14	Hilbich, C. <i>et al.</i> , "Substitutions of Hydrophobic Amino Acids Reduce the Amyloidogenicity of Alzheimer's Disease β A4 Peptides," <i>J. Mol. Biol.</i> 228:460-473 (November 1992).				
	AN	14	Hsu, J.M., <i>et al.</i> , "Zinc Deficiency and Incorporation of 14 C-labeled Methionine into Tissue Proteins in Rats," <i>J. Nutrition</i> 99:425-432 (December 1969).				
	AO	14	Huang, X. <i>et al.</i> , "Zinc-induced Alzheimer's $\text{A}\beta$ 1-40 Aggregation Is Mediated by Conformational Factors," <i>J. Biol. Chem.</i> 272:26464-26470 (October 1997).				
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	AL	<u>15</u>	Jarrett, J.T., <i>et al.</i> , "The Carboxy Terminus of the β Amyloid Protein Is Critical for the Seeding of Amyloid Formation: Implications for the Pathogenesis of Alzheimer's Disease," <i>Biochem.</i> 32:4693-4697 (May 1993).				
	AM	<u>15</u>	Jarrett, J.T., and Lansbury, Jr., P.T., "Amyloid Fibril Formation Requires a Chemically Discriminating Nucleation Event: Studies of an Amyloidogenic Sequence from the Bacterial Protein OsmB," <i>Biochem.</i> 31:12345-12352 (December 1992).				
	AN	<u>15</u>	Johnstone, E.M. <i>et al.</i> , "Conservation of the sequence of the Alzheimer's disease amyloid peptide in dog, polar bear and five other mammals by cross-species polymerase chain reaction analysis," <i>Mol. Brain Res.</i> 10:299-305 (July 1991).				
	AO	<u>15</u>	Joshi, J.G., "Iron and Aluminum Homeostasis in Neural Disorders," <i>Environ. Health Persp.</i> 102:207-213 (1994).				
	AP	<u>15</u>	Kang, J. <i>et al.</i> , "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor," <i>Nature</i> 325: 733-736 (February 1987).				
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	AL	<u>16</u>	Kawahara, M. <i>et al.</i> , "Alzheimer's Disease Amyloid β -Protein Forms Zn^{2+} -Sensitive, Cation-Selective Channels Across Excised Membrane Patches from Hypothalamic Neurons," <i>Biophys. J.</i> 73:67-75 (July 1997).
	AM	<u>16</u>	Kennard, M.L. <i>et al.</i> , "Serum levels of the iron binding protein p97 are elevated in Alzheimer's disease," <i>Nat. Med.</i> 2:1230-1235 (November 1996).
	AN	<u>16</u>	Kidani, Y. <i>et al.</i> , "Mass spectrometry of 5-chloro-7-iodo-8-quinolinol metal chelates," <i>Jpn. Analyst</i> 23:1375-1378 (1974).
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	AP	<u>16</u>	Kirshenbaum, K., and Daggett, V., "pH-Dependent Conformations of the Amyloid β (1-28) Peptide Fragment Explored Using Molecular Dynamics," <i>Biochem.</i> 34:7629-7639 (June 1995).

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	AL	<u>17</u>	Kisilevsky, R., "Inflammation-Associated Amyloidogenesis," <i>Mol. Neurobiol.</i> 8:65-66 (February 1994).
	AM	<u>17</u>	Koh, J.Y., and Choi, D.W., "Quantitative determination of glutamate mediated cortical neuronal injury in cell culture by lactate dehydrogenase efflux assay," <i>J. Neurosci. Meth.</i> 20:83-90 (May 1987).
	AN	<u>17</u>	Kotaki, H., <i>et al.</i> , "Intestinal Absorption and Metabolism of Clloquinol in the Rat," <i>J. Pharm. Dyn.</i> 6:881-887 (November 1983).
	AO	<u>17</u>	Kuo, Y.-M., <i>et al.</i> , "Water-soluble A β (N-40, N-42) Oligomers in Normal and Alzheimer Disease Brains," <i>J. Biol. Chem.</i> 271:4077-4081 (February 1996).
	AP	<u>17</u>	Landers, J.W., and Zak, B., "Determination of Serum Copper and Iron in a Single Small Sample," <i>Am. J. Clin. Pathol.</i> 29:590-592 (June 1958).

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AM	<u>18</u>	Lockhart B.P. <i>et al.</i> , "Inhibitors of free radical formation fail to attenuate direct beta-amyloid ₂₅₋₃₅ peptide-mediated neurotoxicity in rat hippocampal cultures," <i>J. Neurosci. Res.</i> 39:494-505 (November 1994).
AN	<u>18</u>	Lohr, J.B., "Oxygen Radicals and Neuropsychiatric Illness," <i>Arch. Gen. Psychiatry</i> 48:1097-1106 (December 1991).
AO	<u>18</u>	Maggio, J.E., <i>et al.</i> , "Zinc and Alzheimer's Disease," <i>Science</i> 268:1920-1921 (June 1995).
AP	<u>18</u>	Mantyh, P.W., <i>et al.</i> , "Aluminum, Iron, and Zinc Ions Promote Aggregation of Physiological Concentrations of β -Amyloid Peptide," <i>J. Neurochem.</i> 61:1171-1174 (September 1993).

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	AM	<u>20</u>	Menkin, V., "Studies on Inflammation. X. The Cytological Picture of an Inflammatory Exudate in Relation to its Hydrogen Ion Concentration," <i>Am. J. Pathol.</i> 10:193-210 (March 1934).
	AN	<u>20</u>	Michikawa, M., <i>et al.</i> . "Oxygen Radical-Induced Neurotoxicity in Spinal Cord Neuron Cultures," <i>J. Neurosci. Res.</i> 37:62-70 (January 1994).
	AO	<u>20</u>	Milanino, R., <i>et al.</i> , "Copper and the Inflammatory Process," <i>Advances in Inflammation Research</i> 1:281-291 (1979).
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	AM	<u>22</u>	Padmanabhan, G., <i>et al.</i> , "Clioquinol," in: <i>Analytical Profiles of Drug Substances</i> , Volume 18, Florey, K., ed., Academic Press, Inc.: San Diego, CA, pp. 57-90 (1989).
	AN	<u>22</u>	Pérez, A.A. <i>et al.</i> , "Alzheimer Amyloids A β 1-40 and A β 1-42 are Differentially Degraded by Insulin Degrading Enzyme (IDE) From Human Brain," <i>Soc. Neurosci. Abstracts</i> 23:821 (October 1997).
	AO	<u>22</u>	Peters, G., and Rodgers, M.A.J., "Single-Electron Transfer from NADH Analogues to Singlet Oxygen," <i>Biochim. Biophys. Acta</i> 637:43-52 (August 1981).
	AP	<u>22</u>	Pierce, J.E.S., <i>et al.</i> , "Immunohistochemical Characterization of Alterations in the Distribution of Amyloid Precursor Proteins and β -Amyloid Peptide after Experimental Brain Injury in the Rat," <i>J. Neurosci.</i> 16:1083-1090 (February 1996).

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AL	<u>23</u>	Potempa, L.A., <i>et al.</i> , "Effect of Divalent Metal Ions and pH upon the Binding Reactivity of Human Serum Amyloid P Component, a C-reactive Protein Homologue, for Zymosan," <i>J. Biol. Chem.</i> 260:12142-12147 (October 1985).	
AM	<u>23</u>	Richardson, J.S., <i>et al.</i> , "On the Possible Role of Iron-Induced Free Radical Peroxidation in Neural Degeneration in Alzheimer's Disease," <i>Ann. N.Y. Acad. Sci.</i> 648:326-327 (1992).	
AN	<u>23</u>	Roberts, G.W., <i>et al.</i> , "BA4 amyloid protein deposition in brain after head trauma," <i>Lancet</i> 338:1422-1423 (December 1991).	
AO	<u>23</u>	Robinson, S.R. <i>et al.</i> , "Most amyloid plaques contain ferritin-rich cells," <i>Alzheimer's Res.</i> 1:191-196 (1995).	
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AL	<u>24</u>	Roher, A.E., <i>et al.</i> , "Morphology and Toxicity of A β -(1-42) Dimer Derived from Neuritic and Vascular Amyloid Deposits of Alzheimer's Disease," <i>J. Biol. Chem.</i> 271:20631-20635 (August 1996).	
AM	<u>24</u>	Rumble, B. <i>et al.</i> , "Amyloid A4 Protein and Its Precursor in Down's Syndrome and Alzheimer's Disease," <i>New Eng. J. of Med.</i> 320:1446-1452 (June 1989).	
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AO	<u>24</u>	Sano, M., <i>et al.</i> , "A Controlled Trial of Selegiline, Alpha-Tocopherol, or Both as Treatment for Alzheimer's Disease," <i>N.Engl. J. Med.</i> 336:1216-1222 (April 1997).	
AP	<u>24</u>	Sayre, L.M., "Alzheimer's Precursor Protein and the Use of Bathocuproine for Determining Reduction of Copper(II)," <i>Science</i> 274:1933-1934 (December 1996).	

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	AL	<u>25</u>	Schnabel, J., "New Alzheimer's Therapy Suggested," <i>Science</i> 260:1719-1720 (June 1993).
	AM	<u>25</u>	Schubert, D., and Chevion, M., "The Role of Iron in Beta Amyloid Toxicity," <i>Biochem. Biophys. Res. Commun.</i> 216:702-707 (November 1995).
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	AO	<u>25</u>	Seubert, P. <i>et al.</i> , "Isolation and quantification of soluble Alzheimer's β -peptide from biological fluids," <i>Nature</i> 359:325-327 (September 1992).
	AP	<u>25</u>	Shiraki, H., "Neuropathological aspects of the etiopathogenesis of subacute myelo-optico-neuropathy (SMON)," in <i>Handbook of Clinical Neurology. Intoxications of the Nervous System Part II</i> , Vinken, P. J. and Bruyn, G. W., eds., North-Holland Publishing Company, Amsterdam, Holland, pp.141-198 (1979).

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AM	<u>26</u>	Shoji, M. <i>et al.</i> ; "Production of the Alzheimer Amyloid β Protein by Normal Proteolytic Processing," <i>Science</i> 258:126-129 (October 1992).	
AN	<u>26</u>	Sisodia, S.S. <i>et al.</i> , "Cellular and molecular biology of Alzheimer's disease and animal models," <i>Neurodegenerative Diseases</i> 5:59-68 (February 1995).	
AO	<u>26</u>	Skinner, M. <i>et al.</i> , "Observations on the amyloid-degrading activity of serum and its relationship to human neutrophil elastase," <i>Chem. Abst.</i> 101:453, Abstract No. 101:208677n (December 1984).	
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AL	<u>27</u>	Smith, C. <i>et al.</i> , "The molecular pathology of Alzheimer's disease: are we any closer to understanding the neurodegenerative process?," <i>Neuropathol. Appl. Neurobiol.</i> 20:322-38 (August 1994).	
AM	<u>27</u>	Smith, M.A., <i>et al.</i> , "Radical AGEing in Alzheimer's disease," <i>Trends Neurosci.</i> 18:172-176 (April 1995).	
AN	<u>27</u>	Smith M.A., <i>et al.</i> , "Iron accumulation in Alzheimer disease is a source of redox-generated free radicals," <i>Proc. Natl. Acad. Sci. U.S.A.</i> 94:9866-9868 (September 1997).	
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AP	<u>27</u>	Soto, C. <i>et al.</i> , " β -sheet breaker peptides inhibit fibrillogenesis in a rat brain model of amyloidosis: Implications for Alzheimer's therapy," <i>Nature Med.</i> 4:822-826 (July 1998).	

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AL	<u>28</u>	Soto, C., <i>et al.</i> , "Structural Determinants of the Alzheimer's Amyloid β -Peptide," <i>J. Neurochem.</i> 63:1191-1198 (October 1994).
	AM	<u>28</u>	Stankovic, A., and Mitrovic, D.R., "Aluminum Salts Stimulate Luminol-Enhanced Chemiluminescence Production by Human Neutrophils," <i>Free Rad. Res. Comms.</i> 14:47-55 (1991).
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	AP	<u>28</u>	Tamura, Z., "Clinical Chemistry of Clotquinol," <i>Jpn. J. Med. Sci. Biol.</i> 28:69-77 (1975).

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)							
	AL	29	Tateishi, J. <i>et al.</i> , "Strain-differences in dogs for neurotoxicity of clioquinol," <i>Lancet</i> 1:1289-1290 (June 1972).				
	AM	29	Tateishi, J. <i>et al.</i> , "Myeloneuropathy in dogs induced by iodoxyquinoline," <i>Neurology</i> 22:702-709 (July 1972).				
	AN	29	Tateishi, J. <i>et al.</i> , "Autoradiographic Distribution of ¹³¹ I-Clioquinol in Canine and Feline," <i>Folia Psychiatrica et Neurologica Japonica</i> 26:159-164 (1972).				
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	AP	29	Tateishi, J. <i>et al.</i> , "Neurotoxicity of Clioquinol. Part III: Autoradiographic Distribution of Radioactive Clioquinol in Several Species of Animals," <i>Psychiat. Neurol. Jap.</i> 75:187-196 (1973).				
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	AL	<u>30</u>	Tateishi, J. <i>et al.</i> , "Neurotoxicity of Clloquinol in Laboratory Animals," <i>Lancet</i> 2:1095 (November 1972).
	AM	<u>30</u>	Teller, J.K., <i>et al.</i> , "Presence of soluble amyloid β -peptide precedes amyloid plaque formation in Down's Syndrome," <i>Nature Med.</i> 2:93-95 (January 1996).
	AN	<u>30</u>	Terhune, M.W., and Sandstead, H.H., "Decreased RNA Polymerase Activity in Mammalian Zinc Deficiency," <i>Science</i> 177:68-69 (July 1972).
	AO	<u>30</u>	Thomas, T., <i>et al.</i> , " β -Amyloid-mediated vasoactivity and vascular endothelial damage," <i>Nature</i> 380:168-171 (March 1996).
	AP	<u>30</u>	Tomiyama, T., <i>et al.</i> , "Rifampicin Prevents the Aggregation and Neurotoxicity of Amyloid β Protein <i>In Vitro</i> ," <i>Biochem. Biophys. Res. Comm.</i> 204:76-83 (October 1994).

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	AM	<u>31</u>	Thompson, C.M. <i>et al.</i> , "Regional Brain Trace-Element Studies in Alzheimer's Disease," <i>NeuroToxicol.</i> 9:1-8 (1988).
	AN	<u>31</u>	Tomski, S.J., and Murphy, R.M., "Kinetics of Aggregation of Synthetic β -Amyloid Peptide," <i>Arch. Biochem. Biophys.</i> 294:630-638 (May 1992).
	AO	<u>31</u>	Treuhaft, P.S., and McCarty, D.J., "Synovial Fluid pH, Lactate, Oxygen and Carbon Dioxide Partial Pressure in Various Joint Diseases," <i>Arth. Rheum.</i> 4:475-484 (July-August 1971).
	AP	<u>31</u>	Van Nostrand, W.E., "Zinc (II) Selectively Enhances the Inhibition of Coagulation Factor XIa by Protease Nexin-2/Amyloid β -Protein Precursor," <i>Thrombosis Res.</i> 78:43-53 (April 1995).

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	AN	<u>32</u>	Wood, S.J., <i>et al.</i> , "Physical, Morphological and Functional Differences between pH 5.8 and 7.4 Aggregates of the Alzheimer's Amyloid Peptide A β ," <i>J. Mol. Biol.</i> 256:870-877 (March 1996).
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AM	<u>33</u>	Linert, W. <i>et al.</i> , "Dopamine, 6-hydroxydopamine, iron, and dioxygen-their mutual interaction and possible implication in the development of Parkinson's disease," <i>Biochim. Biophys. Acta</i> 1316:160-168 (August 1996).
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BUSH *et al.*

Appl. No. 09/380,704

Filed: September 8, 1999

For: **Identification of Agents for Use in
the Treatment of Alzheimer's
Disease**

Art Unit: To be assigned

Examiner: To be assigned

Atty. Docket: 0609.4350001/REF/KKV

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First Supplemental Information Disclosure Statement

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. A copy of each document is submitted herewith. The numbering on this First Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Information Disclosure Statement filed on January 18, 2000 in connection with the above-captioned application.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior

MAR 14, 2000

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BUSH *et al.*
Appl. No. 09/380,704

art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This First Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. No statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this pleading is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Kristin K. Vidovich

Kristin K. Vidovich
Attorney for Applicants
Registration No. 41,448

Date: March 14, 2000

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Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

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Page 1 of 2

FORM PTO-1449

ATTY. DOCKET NO.
0609.4350001/REF/KKV

APPLICATION NO.
09/380,704

FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

APPLICANT
BUSH *et al.*

FILING DATE
September 8, 1999

GROUP
To be assigned

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA2	5,357,636	10/25/1994	Dresdner, Jr. <i>et al.</i>	2	161.7	06/30/1992
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AI						Yes No
	AJ						Yes No
	AK						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AL

AM

AN

AO

AP

33

Nakada, T. and I.L. Kwee, "Guanidinoethane sulfate: brain pH alkaline shifter," *NeuroReport* 4:1035-1038 (August 1993)

EXAMINER

DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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Rev. 1/95

MAR 14, 2000

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Page 2 of 2

FORM PTO-1449

FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO.
0609.4350001/REF/KKV

APPLICATION NO.
09/380,704

APPLICANT
BUSH *et al.*

FILING DATE
September 8, 1999

GROUP
To be assigned

U.S. PATENT DOCUMENTS

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	AH						

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AI						Yes No
	AJ						Yes No
	AK						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AL	34	Schrader-Fischer, G. and P.A. Paganetti, "Effect of alkalizing agents on the processing of the β -amyloid precursor protein," <i>Brain Research</i> 716:91-100 (April 1996)
	AM		
	AN		
	AO		
	AP		

EXAMINER	DATE CONSIDERED
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EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Bush *et al.*

Appl. No. 09/380,704

102(e) Date: June 6, 2000

For: **Identification of Agents for Use in
the Treatment of Alzheimer's
Disease**

Art Unit: 1614

Examiner: To Be Assigned

Atty. Docket: 0609.4350001/REF/KKV

Second Supplemental Information Disclosure Statement

Commissioner for Patents
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Second Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' First Supplemental Information Disclosure Statement filed on March 14, 2000 in connection with the above-captioned application.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be

AUG. 14, 2000

COPY

- 2 -

Bush *et al.*
Appl. No. 09/380,704

prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. No statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this pleading is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Kristin K. Vidovich

Kristin K. Vidovich
Attorney for Applicants
Registration No. 41,448

Date: August 14, 2000

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

COPY

Page 1 of 5

FORM PTO-1449

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO.
0609.4350001

APPLICATION NO.
09/380,704

APPLICANT
Bush *et al.*

102 (e) DATE
June 6, 2000

GROUP
1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA						
	AB						
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	AG						
	AH						

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AI						Yes No
	AJ						Yes No
	AK						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AL	<u>34</u>	
	AM	<u>34</u>	Atwood, C.S. <i>et al.</i> , "Copper-Mediated Aggregation And Polymerization of A β ," <i>Soc. Neurosci. Abstr.</i> 23:1883 (October 1997).
	AN	<u>34</u>	Bruijn, L.I., <i>et al.</i> , "ALS-Linked SOD1 Mutant G85R Mediates Damage to Astrocytes and Promotes Rapidly Progressive Disease with SOD1-Containing Inclusions," <i>Neuron</i> 18:327-338 (February 1997).
	AO	<u>34</u>	Ceballos-Picot, I., <i>et al.</i> , "Peripheral Antioxidant Enzyme Activities And Selenium In Elderly Subjects And In Dementia Of Alzheimer's Type--Place Of The Extracellular Glutathione Peroxidase," <i>Free Radic. Biol. Med.</i> 20:579-587 (1996).
	AP	<u>34</u>	Chan, C.-W., <i>et al.</i> , "Anti-apoptotic action of Alzheimer A β ," <i>Alzheimer's Reports</i> 2:113-119 (March 1999).

EXAMINER

DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

AUG. 14, 2000

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Page 2 of 5

FORM PTO-1449

ATTY. DOCKET NO.
0609.4350001

APPLICATION NO.
09/380,704

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

APPLICANT
Bush et al.

102 (e) DATE
June 6, 2000

GROUP
1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA						
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FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AI						Yes No
	AJ						Yes No
	AK						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AL	35	Cohen, A.S., "Amyloidosis," <i>Arthritis and Allied Conditions- A Textbook of Rheumatology</i> , D.J. McCarty, ed., Lea and Febiger, Philadelphia, pp. 1273-1293 (1989).
AM	35	Garzon-Rodriguez, W., et al., "Soluble Amyloid A β -(1-40) Exists as a Stable Dimer at Low Concentrations," <i>J. Biol. Chem.</i> 272:21037-21044 (August 1997).
AN	35	Goto, J.J., et al., "Reactions of Hydrogen Peroxide with Familial Amyotrophic Lateral Sclerosis Mutant Human Copper-Zinc Superoxide Dismutases Studied by Pulse Radiolysis," <i>J. Biol. Chem.</i> 273:30104-30109 (November 1998).
AO	35	Huang, X., et al., "The A β Peptide of Alzheimer's Disease Directly Produces Hydrogen Peroxide through Metal Ion Reduction," <i>Biochemistry</i> 38:7609-7616 (June 1999).
AP	35	Kisilevsky, R., "Amyloidosis: A Familiar Problem in the Light of Current Pathogenetic Developments," <i>Lab. Invest.</i> 49:381-390 (October 1983).

EXAMINER

DATE CONSIDERED

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Page 3 of 5

FORM PTO-1449

ATTY. DOCKET NO.
0609.4350001APPLICATION NO.
09/380,704

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

APPLICANT
Bush *et al.*102(e) DATE
June 6, 2000GROUP
1614

U.S. PATENT DOCUMENTS

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	AI						Yes No
	AJ						Yes No
	AK						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AL	<u>36</u>	Kuo, Y.-M., <i>et al.</i> , "High Levels of Circulating A β 42 Are Sequestered by Plasma Proteins in Alzheimer's Disease," <i>Biochem. Biophys. Res. Commun.</i> 257:787-791 (April 1999).
AM	<u>36</u>	Lovell, M.A., <i>et al.</i> , "Copper, iron and zinc in Alzheimer's disease senile plaques," <i>J. Neurol. Sci.</i> 158:47-52 (June 1998).
AN	<u>36</u>	Martins, R.N., <i>et al.</i> , "Increased Cerebral Glucose-6-Phosphate Dehydrogenase Activity in Alzheimer's Disease May Reflect Oxidative Stress," <i>J. Neurochem.</i> 46:1042-1045 (April 1986).
AO	<u>36</u>	Kang, J., <i>et al.</i> , "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor," <i>Nature</i> 325:733-736 (February 1987).
AP	<u>36</u>	Nunomura, A., <i>et al.</i> , "RNA Oxidation Is a Prominent Feature of Vulnerable Neurons in Alzheimer's Disease," <i>J. Neurosci.</i> 19:1959-1964 (March 1999).

EXAMINER

DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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Page 4 of 5

FORM PTO-1449 SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0609.4350001	APPLICATION NO. 09/380,704
APPLICANT Bush <i>et al.</i>		
102 (e) DATE June 6, 2000		GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	AA	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
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FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	AI	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AI						Yes No
	AJ						Yes No
	AK						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AL	<u>37</u>	Pepys, M.B. and Baltz, M.L., "Acute Phase Proteins with Special Reference to C-Reactive Protein and Related Proteins (Pentaxins) and Serum Amyloid A Protein," in <u>Advances in Immunology</u> , Vol. 34, pp.141-212 (1983).
	AM	<u>37</u>	Raby, C.A., <i>et al.</i> , "Traumatic Brain Injury Increases β -Amyloid Peptide 1-42 in Cerebrospinal Fluid," <u>J. Neurochem.</u> 71:2505-2509 (December 1998).
	AN	<u>37</u>	Rosen, D., <i>et al.</i> , "Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis," <u>Nature</u> 362:59-62 (March 1993).
	AO	<u>37</u>	Smith, M. A., <i>et al.</i> , "Oxidative damage in Alzheimer's," <u>Nature</u> 382:120-121 (July 1996).
	AP	<u>37</u>	Suzuki, N., <i>et al.</i> , "An Increased Percentage of Long Amyloid β -Protein Secreted by Familial Amyloid β -Protein Precursor (BAPP ₇₁) Mutants," <u>Science</u> 264:1336-1340 (May 1994).

EXAMINER	DATE CONSIDERED
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EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449

ATTY. DOCKET NO.
0609.4350001APPLICATION NO.
09/380,704

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

APPLICANT
Bush *et al.*102 (e) DATE
June 6, 2000GROUP
1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA						
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FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AI						Yes No
	AJ						Yes No
	AK						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AL	<u>38</u>	Terry, R.D., <i>et al.</i> , "Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment," <i>Ann. Neurol.</i> 30:572-580 (October 1991).
AM	<u>38</u>	Uchida, K. and Kawakishi, S., "Identification of oxidized Histidine Generated at the Active Site of Cu,Zn-Superoxide Dismutase Exposed to H ₂ O ₂ . Selective Generation Of 2-Oxo-Histidine At The Histidine 118," <i>J. Biol. Chem.</i> 269:2405-2410 (January 1994).
AN	<u>38</u>	Wolozin, B., <i>et al.</i> , "Participation of presenilin 2 in Apoptosis: Enhanced Basal Activity Conferred by an Alzheimer Mutation," <i>Science</i> 274:1710-1713 (December 1996).
AO	<u>38</u>	Yankner, B.A., <i>et al.</i> , "Neurotrophic and Neurotoxic Effects of Amyloid β Protein: Reversal by Tachykinin Neuropeptides," <i>Science</i> 250:279-282 (October 1990).
AP	<u>38</u>	Yim, M.B., <i>et al.</i> , "A gain-of-function of an amyotrophic lateral sclerosis-associated Cu,Zn-superoxide dismutase mutant: An enhancement of free radical formation due to a decrease in K _m for hydrogen peroxide," <i>Proc. Natl. Acad. Sci. USA</i> 93:5709-5714 (June 1996).

EXAMINER

DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Bush *et al.*

Appl. No. 09/380,704

102(e) date: June 6, 2000

For: **Identification of Agents for Use in
the Treatment of Alzheimer's
Disease**

Art Unit: 1614

Examiner: To Be Assigned

Atty. Docket: 0609.4350001/JAG/HLK

Third Supplemental Information Disclosure Statement

Commissioner for Patents
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Third Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Second Supplemental Information Disclosure Statement filed on August 14, 2000 in connection with the above-captioned application. A copy of each document is also provided.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates

should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

Applicants have checked the appropriate boxes below.

- ☒ 1. This Information Disclosure Statement is being filed within three months of the U.S. filing date OR before the mailing date of a first Office Action on the merits. No statement or fee is required.
- ☐ 2. This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection or Notice of Allowance.
 - ☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

- ☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).
- ☐ c. Attached is our Check No. _____ in the amount of \$ _____ in payment of the fee under 37 C.F.R. § 1.17(p).
- ☐ 3. This Information Disclosure Statement is being filed more than three months after the U.S. filing date and after the mailing date of a Final Rejection or Notice of Allowance, but before payment of the Issue Fee. Enclosed find our Check No. _____ in the amount of \$ _____ in payment of the fee under 37 C.F.R. § 1.17(p).
- ☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).
- ☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).
- ☐ 4. The document(s) was/were cited in a search report by a foreign patent office in a counterpart foreign application. Submission of an English language version of the search report that indicates the degree of relevance found by the foreign office is provided in satisfaction of the requirement for a concise explanation of relevance. 1138 OG 37, 38.

COPY

Bush *et al.*
Appl. No. 09/380,704

- 4 -

- ☐ 5. A concise explanation of the relevance of the non-English language document(s) appears below:
- ☐ 6. The Examiner's attention is directed to co-pending U.S. Patent Application No. _____, filed _____, which is directed to related technical subject matter. The identification of this U.S. Patent Application is not to be construed as a waiver of secrecy as to that application now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited application and the art cited therein during examination.
- ☐ 7. Copies of the documents were cited by or submitted to the Office in Application No. _____, filed _____, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d).

It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

COPY


- 5 -

Bush *et al.*
Appl. No. 09/380,704

A duplicate copy of this pleading is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.


Reg. No. 34,395

Heidi L. Kraus
Attorney for Applicants
Registration No. 43,730

Date: November 30, 2000
1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

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Page 1 of 1

FORM PTO-1449

ATTY. DOCKET NO.
0609.4350001

APPLICATION NO.
09/380,704

THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

APPLICANT
Bush *et al.*

102 (e) DATE
June 6, 2000

GROUP
1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA						
	AB2	5,927,283	07/27/1999	Abraham <i>et al.</i>	128	898	05/08/1997
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AI						Yes No
	AJ						Yes No
	AK5	WO 99/18432	04/15/1999	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AL	<u>39</u>	Atwood, C.S. <i>et al.</i> , "Role of Free Radicals and Metal Ions in the Pathogenesis of Alzheimer's Disease," in <i>Metal Ions in Biological Systems</i> , Sigel, A. and Sigel H., eds., Vol. 36, Ch. 10, Marcel Dekker Inc., New York, pp. 309-364 (1999).
	AM	<u>39</u>	McKeon-O'Mally, C., <i>et al.</i> , "Potential Therapeutic Targets for Alzheimer's Disease," <i>Emerging Therapeutic Targets</i> 2:157-179, Ashley Publications Ltd. (1998).
	AN	<u>39</u>	International Search Report for PCT/US00/11715, mailed August 30, 2000.
	AO		
	AP		

EXAMINER

DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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NOV 30, 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Bush *et al.*

Appl. No. 09/380,704

102(e) Date: June 6, 2000

For: **Identification of Agents for Use in
the Treatment of Alzheimer's
Disease**

Art Unit: 1614

Examiner: to be assigned

Atty. Docket: 0609.4350001/JAG/KKV

COPY

Fourth Supplemental Information Disclosure Statement

Commissioner for Patents
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this fourth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' third Information Disclosure Statement filed on November 30, 2000, in connection with the above-captioned application. A copy of each document is provided.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

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COPY

- 2 -

Bush *et al.*
Appl. No. 09/380,704

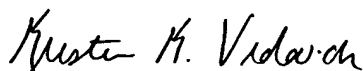
art, and/or to prove that this information may not be enabling for the teachings purportedly offered. This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. No statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this pleading is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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INFORMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO.
0609.4350001/JAG/KKV

APPLICATION NO.
09/380,704

APPLICANT
Bush *et al.*

102(e) Date
June 6, 2000

GROUP
1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA2						
	AB2						
	AC2	5,110,493	05/05/1992	Cherng-Chyi <i>et al.</i>	514	413	
	AD2	5,466,680	11/14/1995	Rudy	514	57	
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AO	<u>39</u>	Gutierrez-Correa, J. and A.O.M. Stoppani, Free Rad. Res. 22(3): 239-250 (March 1995) (publisher: Harwood Academic Publishers GmbH)
	AP	<u>39</u>	Lodemann, E., Naturwissenschaften 66(9): 462-466 (September 1979) (publisher: Springer-Verlag)
	AL	<u>40</u>	Sue, Y.-J. <i>et al.</i> , Annals of Emergency Medicine 24(4): 709-712 (October 1994) (publisher: American College of Emergency Physicians)

EXAMINER

DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

DEC 27, 2000